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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,216	09/19/2003	Shaker A. Mousa	MOUS-4618	7027

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SCHMEISER, OLSEN & WATTS
22 CENTURY HILL DRIVE
SUITE 302
LATHAM, NY 12110

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/667,216	MOUSA, SHAKER A.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,43,49-54,56-59 and 61-94* is/are pending in the application.

4a) Of the above claim(s) *64-90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11 Aug 2008 has been entered.

Claims 1, 2, 5, 6, 43, 49-54, 56-59 and 61-94 are pending in the current application. Claims 64-90, drawn to a non-elected invention, are withdrawn.

Objections Withdrawn

Applicant's Amendment, filed 11 Aug 2008, with respect to objections to claim 54 has been fully considered and is persuasive, as the identified informality is corrected and "thiotepa" is an accepted name in the art.

This objection has been **withdrawn**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims 1, 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 are drawn to an oxidized heparin fraction having a molecular weight of from about 2,000 to about 4,000 daltons, wherein the oxidized heparin fraction is super-sulfated.

The recitations in:

claim 1: "wherein the oxidized heparin fraction is super-sulfated such that the super-sulfated oxidized heparin fraction comprises an anticoagulant reduction characteristic and an angiogenesis inhibition characteristic", and "wherein the super-sulfated oxidized heparin fraction fully inhibits fibroblast growth factor (FGF2) induced angiogenesis";

claim 93: "wherein the anticoagulant reduction characteristic comprises a first anticoagulant reduction characteristic, a second anticoagulant reduction characteristic, or a combination thereof;

wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood;

wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT); and wherein the angiogenesis inhibition characteristic is that the oxidized heparin fraction in an endothelial cell (EC) growth medium cancels an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condtion condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of at least about 2 if the oxidized heparin fraction is not in the EC growth medium";

claim 2: "wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic";

claim 5: "wherein the anticoagulant reduction characteristic comprises the second anticoagulant reduction characteristic"; and

claim 6: "wherein the anticoagulant reduction characteristic comprises the first anticoagulant reduction characteristic and the second anticoagulant reduction characteristic";

are seen to be merely functional language.

Applicant's Remarks, filed 11 Aug 2008, at page 20, paragraph 5, indicate the functional language is intended to distinguish the instantly claimed compound from the genus of compound of super-sulfated oxidized heparin fractions.

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus..." at 1406 (emphases added).

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co*. Hence, in the absence of fully recognizing the identity of the members of the genus herein, one of skill in the art would be unable to fully predict structural requirements, formula, or chemical name of any compounds having claimed the functional properties herein within the broad genus of super-sulfated oxidized heparin fractions.

Claims 49-54 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The recitations in:

Claim 49: non-heparin anticoagulant;

Claim 50: anti-Xa compounds, anti-IIa compounds, anti-tissue factor compounds, anti-VIIa compounds;

Claim 51: a non-heparin angiogenic inhibitor;

Claim 52: integrin inhibitory compounds, fibroblast growth factor inhibitors, fibroblast growth factor receptor inhibitors, vascular endothelial growth factor inhibitors;

Claim 53: a cytotoxic or chemotherapeutic agent;

Claim 54: non-classic alkylators, antitumor antibiotics, microtubule agents;

are seen to be merely functional language. The above recitations define chemical compounds or classes of chemical compounds by their biochemical functions.

Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate". The CAFC further clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus..." at 1406 (emphases added).

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the

more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having the claimed functional properties in the pharmaceutical compositions herein.

Thus, Applicants functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

Claim 54 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 54 recites "platinum complexes" and "substituted urea".

The specification does not disclose specific platinum complexes and urea with substituents which meet the written description and enablement provisions of 35 USC

112, first paragraph. However, claim 54 is directed to encompass complexes and substituents, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these platinum complexes or substituted ureas meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and because chemical complexes and substituents are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim. The specification provides only the written description of the structural features of platinum in the platinum complexes and urea in the substituted urea, and the functional definition that the compounds are cytotoxic or chemotherapeutic at page 20, paragraph 57.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical

structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the structurally defined chemical compounds, but not the full breadth of the claims, meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See Vas-Cath at page 1115.)

The court of *In re Curtis* held that "a patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when... the evidence indicates ordinary artisans could not predict the operability ... of any other species." (see *In re Curtis* 354 F.3d 1347, 69 USPQ2d 1274,

Fed. Cir. 2004). The court of *Noelle v. Lederman* also pointed out that generic claim to anti-CD40CR Mabs lacked written description support because there was no description of anti-human or other species Mabs, and no description of human CD40CR antigen. The court further pointed out that attempt to "define an unknown by its binding affinity to another unknown" failed. See 355 F.3d 1343, 69 USPQ2d 1508, Fed. Cir. 2004.

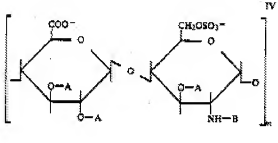
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 1, 2, 5, 6, 43, 91-94 are rejected under 35 U.S.C. 102(b) as being anticipated by Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record). Definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service (Massachusetts General Hospital Pathology Service, cited in PTO-892) provide evidence regarding the Activated Partial Thromboplastin Time and Anti-Xa disclosed by Naggi et al.

Naggi et al. discloses the structure as formula IV,



, wherein m is an integer from 4 to 15, A is H or

SO_3^-, and B is SO_3^- or $COCH_3$ (column 6, lines 1-19). Naggi et al. discloses a broader disclosure of depolymerized and supersulfated heparin having a molecular weight between 2000 and 9000 and a sulfation degree of at least 2.5 and the process for its preparation comprising sulfating heparin (abstract). Naggi et al. discloses a preferred sulfation degree of from 3.0±0.1 to 3.3±0.1 (column 6, lines 54-57). Naggi et al. discloses a preferred embodiment of depolymerized and supersulfated heparin wherein the molecular weight is 3000-5000 and the sulfation degree is 2.6 (example 12 at column 12, lines 1-30), or a heparin fraction wherein 52% of the primary and secondary hydroxyl groups are substituted by O-sulfate esters, meeting limitations of instant claim 1, 2, 5, 6, 91-93. The term "sulfate to carboxylate ratio of about 5:1" in instant claim 91 broadens the ratio without guidance as to the range encompassed by the term "about", and the disclosed sulfation degree of 2.6, or ratio of sulfate to carboxylate of 2.6:1, is interpreted to be about 5:1 because it is the same order of magnitude. Naggi et al. discloses the compound in the form of a pharmaceutical composition (column 10, lines 55-57), or a composition comprising about 100% of the depolymerized and supersulfated heparin and about 0% of heparin, low molecular weight heparin, chondroitin sulfates, dermatan sulfates, heparan sulfates, heparin derivatives, or combinations thereof, meeting the limitations of instant claim 43. Naggi et al. discloses the heparin treated with sulfuric acid and chlorosulfonic acid, a strong oxidizing agent, to depolymerize and super-sulfate heparin (example 12 at column 12, lines 1-30), which necessarily encompasses the reaction sequence comprising the steps of oxidizing said heparin in order to depolymerize said heparin and then performing sulfate substitution at

oxygen bonds within repeating units of said oxidized depolymerized heparin to produce the super-sulfated heparin of formula IV, meeting the instant limitations of instant claim 94.

Naggi et al. discloses the reduction of the anticoagulation reduction characteristic with regards to the activated partial thromboplastin time (APTT) (column 9, lines 7-11 and 47-60), meeting the limitations of instant claims 5 and 93. Definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service show that determination of levels of anticoagulation are known in the art to be acceptably measured in terms of units/mL (Heparin Antifactor Xa Assay, page 2, sections **Reference Interval** and **Use**) in addition to times. The definition of Activated Partial Thromboplastin Time from Massachusetts General Hospital Pathology Service shows the Heparin Antifactor Xa Assay is an equivalent assay to the measurement of Activated Partial Thromboplastin Time (Activated Partial Thromboplastin Time, parage 2, section **Limitations**.) The depolymerized and supersulfated heparin disclosed by Naggi et al. shows a reduction of the APTT or Anti-Xa as measured in terms of units/mL in table I (column 9, lines 50-65) for products AH-17 and AH-19, relative to the heparin D-212, the reduction being approximately 76.5% (0.05 U/ml / 0.212 U/ml) for the same dose (50 IU/kg), or a reduced prolongation of clotting time of human blood by at least 75% relative to the prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the

unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT).

Naggi et al. is silent as to an angiogenesis inhibition characteristic and the anticoagulant reduction characteristic in terms of a "percent inhibition of platelet clot strength," but does recite that the depolymerized and supersulfated heparin shows a weak anticoagulant activity (column 5, lines 41-45), providing evidence tending to show inherency when combined with said activity measured with regard to APTT and Anti-Xa. Therefore it is apparent from what is disclosed that the functional characteristics recited in instant claims 2 and 6 are inherent in the compound disclosed by Naggi et al.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claim 1 recites the product-by-process, "wherein the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction..." "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or

obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Response to Applicant's Remarks:

Applicant's Remarks, filed on 11 Aug 2008, have been fully considered and not found to be persuasive.

Applicant asserts that the depolymerized and supersulfated heparin disclosed by Naggi et al., produced by a different process than the instant super-sulfated oxidized heparin fraction, is not an identical or substantially identical product. Applicant indicates table 3 on page 29, which details functional properties of the instant super-sulfated oxidized heparin fraction, as supporting this assertion. However, table 3 on page 29 does not provide any structural information regarding the instant super-sulfated oxidized heparin fraction, nor does it identify what structural properties are required by the disclosed functional properties. Therefore these disclosed functional properties, absent any structural information regarding the instant super-sulfated oxidized heparin fraction,

are not persuasive to show that the depolymerized and supersulfated heparin disclosed by Naggi et al. is not an identical or substantially identical product to the instantly claimed product.

Applicant asserts that because Naggi does not explicitly disclose that the depolymerized and supersulfated heparin disclosed by Naggi et al. does not fully inhibit FGF2 induced angiogenesis then the depolymerized and supersulfated heparin disclosed by Naggi et al. does not anticipate the instantly claimed product. As recited above, it is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph). See also MPEP 2112.01 II., "A chemical composition and its properties are inseparable." Absent a showing of evidence that the that the depolymerized and supersulfated heparin disclosed by Naggi et al. is not an identical or substantially identical product to the instantly claimed product, the properties of the product disclosed by Naggi et al. are necessarily the same as the properties of the instantly claimed product, including the property of physiological activity.

Applicant provides evidence by way of Lundin teaching desulfation for inhibiting angiogenesis. However, "There is no requirement that a person of ordinary skill in the

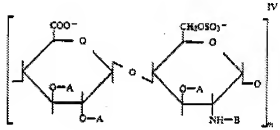
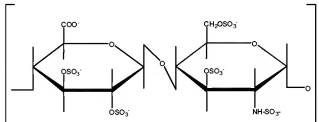
art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference", see MPEP 2112 II.

At pages 22-24 Applicant again asserts the the depolymerized and supersulfated heparin disclosed by Naggi et al., produced by a different process than the instant super-sulfated oxidized heparin fraction, is not an identical or substantially identical product. However absent any structural information regarding the instant super-sulfated oxidized heparin fraction, these remarks not persuasive to show that the depolymerized and supersulfated heparin disclosed by Naggi et al. is not an identical or substantially identical product to the instantly claimed product with properties that are necessarily the same as the properties of the instantly claimed product, including the property of physiological activity.

As recited above, relying upon definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service (Massachusetts General Hospital Pathology Service, cited in PTO-892), the disclosure of APTT by Naggi et al. in terms of units of U/ml instead of units of time is an accepted use in the art as a way of measuring APTT and Anti-Xa anticoagulation activity.

Applicant remarks that the recitation of Naggi et al. that the depolymerized and supersulfated heparin shows a weak anticoagulant activity does not teach the instantly claimed functional property. Applicant remarks that the instantly claimed functional property cannot be concluded from the disclosed weak anticoagulant activity. However, this disclosed property is relied upon as additional evidence that the instantly claimed

functional property is a necessarily inherent property of an identical or substantially identical chemical composition, not as direct evidence of the instantly claimed functional property. The functional property of EC tube formation is also a necessarily inherent property of an identical or substantially identical chemical composition.

With regard to formula IV,  wherein m is an integer from 4 to 15, A is H or SO_3^-, and B is SO_3^-or $COCH_3$ (column 6, lines 1-19), the compound encompassed in this disclosure wherein m is 4 and A and B are SO_3^-, shown as  , contains 5 sulfates and 1 carboxylate, which is a sulfate to carboxylate ratio of 5:1.

Applicant asserts that the method disclosed by Naggi et al. does not disclose a first oxidized fraction prior to O-sulfation, in the generation of the O-sulfated depolymerized heparin disclosed by Naggi et al. Naggi et al. discloses the heparin treated with sulfuric acid and chlorosulfonic acid, a strong oxidizing agent, to depolymerize and super-sulfate heparin (example 12 at column 12, lines 1-30), which necessarily encompasses the reaction sequence comprising the steps of oxidizing said heparin in order to depolymerize said heparin and then performing sulfate substitution at

oxygen bonds within repeating units of said oxidized depolymerized heparin to produce the super-sulfated heparin of formula IV, meeting the instant limitations of instant claim 94. Naggi et al. discloses that it is well known in the art that the process of depolymerizing heparin, such as by oxidation using acid and a strong oxidizing agent such as hydrogen peroxide (column 4, lines 10-20), occurs prior to sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin, and it is the invention of Naggi et al. to perform sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin (column 5, lines 5-30). Therefore the existence of the first oxidized fraction prior to O-sulfation is implicitly present as a reaction intermediate in the process disclosed by Naggi et al.

Therefore, absent an evidentiary showing that the depolymerized and supersulfated heparin disclosed by Naggi et al. is not an identical or substantially identical product to the instantly claimed product or proving that subject matter shown to be in the prior art Naggi et al. does not possess the characteristic relied on, this rejection is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended claims 1, 43, 49, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) in view of Weitz et al. (US Patent 6,075,013, issued 13 Jun 2000, of record).

Naggi et al. discloses as above.

Naggi et al. does not disclose the specific composition further comprising a non-heparin anticoagulant.

Weitz et al. teaches the use of modified low molecular weight heparin (column 10, lines 25-30) obtained by oxidation (column 10, lines 47-53) used in conjunction with conventional thrombolytic treatments, such as tissue plasminogen activator, an anti-tissue factor compound (column 11, lines 20-30).

It would have been obvious to one of ordinary skill at the time of the invention to combine depolymerized and supersulfated heparin disclosed by Naggi et al. in conjunction with conventional thrombolytic treatments, such as tissue plasminogen activator, an anti-tissue factor compound, as taught by Weitz et al. Both inventions are drawn to antithrombotic compositions. See MPEP 2144.06, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."

Response to Applicant's Remarks:

Applicant's Remarks, filed on 11 Aug 2008, have been fully considered and not found to be persuasive.

The response to Applicant's remarks regarding Naggi et al. is as detailed above.

Amended claims 1 and 56-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) in view of Conrad et al. (US Patent 5,280,016, issued 18 Jan 1994, of record).

Naggi et al. discloses as above.

Naggi et al. does not specifically disclose a polymeric structure comprising an oxidized heparin fraction, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting or copolymerization, non-covalently incorporated into a matrix of the polymeric structure, or encapsulated as a biomedical material within the polymeric structure, or wherein said biocompatible polymer is ethylene vinyl acetate.

Conrad et al. teaches size separated fractions of depolymerized low molecular weight heparin produced by periodate oxidation (column 3, lines 25-29) that are non-anticoagulant and show antiproliferative activity with respect to smooth muscle cells (abstract), or an angiogenesis inhibition characteristic. Conrad et al. teaches the size separated fractions are treated chemically to produce O-oversulfation to increase activity (column 4, lines 27-37). Conrad et al. teaches the heparin administered in the form of an implant containing biodegradable polymer materials such as collagen, formulated as patches or beads, which is encapsulation as a biomedical material, or by local administration through a continuous release device such as a supporting matrix, which is understood to be non-covalent incorporation into the matrix (column 10, lines

47-50 and 60-63). Conrad et al. teaches the use of the specific polymer ethylene vinyl acetate as the supporting matrix (column 14, lines 34-38).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the depolymerized and supersulfated heparin disclosed by Naggi et al. with the O-oversulfated low molecular weight heparin incorporated into a polymeric structure as taught by Conrad et al. Conrad et al. teaches the size separated fractions are treated chemical to produce O-oversulfation to increase activity (column 4, lines 27-37). Naggi et al. recites "It is also generally recognized that at the same degree of polymerization, the biological activity of polysaccharides increases with their sulfation degree," (column 3, lines 42-44). Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to use of a known technique of supersulfation to improve similar depolymerized low molecular weight heparin in the same way by combining the depolymerized and supersulfated heparin disclosed by Naggi et al. with the O-oversulfated low molecular weight heparin incorporated into a polymeric structure as taught by Conrad et al.

Response to Applicant's Remarks:

Applicant's Remarks, filed on 11 Aug 2008, have been fully considered and not found to be persuasive.

The response to Applicant's remarks regarding Naggi et al. is as detailed above.

Amended claims 1, 43 and 51-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) in

view of Conrad et al. (US Patent 5,280,016, issued 18 Jan 1994, of record) as applied to claims 1 and 56-59 above, and further in view of Kerbel et al. (Cancer and Metastasis Reviews, 2001, 20, p79-86, of record).

Naggi et al. in view of Conrad et al. discloses as above. Conrad et al. makes explicit that the antiproliferative activity with respect to smooth muscle cells, or angiogenesis inhibition characteristic, inherent in the compound disclosed by Naggi et al. was recognized in the prior art.

Naggi et al. in view of Conrad et al. does not disclose the specific composition further comprising a non-heparin angiogenic inhibitor, or a cytotoxic or chemotherapeutic agent.

Kerbel et al. teaches the use of combinations of angiogenesis inhibitors (page 82, right column, lines 9-11), such as chemotherapy drugs such as microtubule agents and anti-angiogenic drugs (page 82, right column, lines 14-17). Kerbel et al. teaches the use of combinations of specific drugs such as DC101 antibody to VEGF (vascular endothelial growth factor) receptor-2 (page 83, spanning left column line 23 and right column lines 1-2); thalidomide, interferon alpha, and low molecular weight heparin (page 83, right column, lines 18-22) and angiostatin, endostatin, and interleukin-12 (page 84, left column, lines 1-3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the depolymerized and supersulfated heparin taught by Naggi et al. in view of Conrad et al. with the combinations of angiogenesis inhibitors taught by Kerbel et al. See MPEP 2144.06, "It is *prima facie* obvious to combine two

compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." Kerbel et al. teaches the use of low molecular weight heparin in said combinations. One of ordinary skill in the art would be motivated to combine the specific depolymerized and supersulfated heparin taught by Naggi et al. in view of Conrad et al. with the combinations of angiogenesis inhibitors taught by Kerbel et al. because Naggi et al. recites "It is also generally recognized that at the same degree of polymerization, the biological activity of polysaccharides increases with their sulfation degree," (column 3, lines 42-44).

Response to Applicant's Remarks:

Applicant's Remarks, filed on 11 Aug 2008, have been fully considered and not found to be persuasive.

The response to Applicant's remarks regarding Naggi et al. is as detailed above.

Amended claims 1, 56, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) in view of Scholander (US Patent 6,461,665, issued 08 Oct 2002, of record).

Naggi et al. discloses as above.

Naggi et al. does not disclose the polymeric structure wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting or by copolymerization.

Scholander teaches a surface modified to have improved antithrombogenic activity by attaching heparin to the surface to be modified (abstract), comprising reacting heparin with the surface (column 4, lines 25-40), or surface grafting, or by reacting the heparin with a polymer layer and reacting the heparin-containing polymer with other polymers (column 5, lines 1-30), such as when the heparin is reacted with the later from step (a). The reaction of a heparin-containing polymer with other polymers can be interpreted as copolymerization.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the depolymerized and supersulfated heparin disclosed by Naggi et al. with the surface modified to have improved antithrombogenic activity by attaching heparin to the surface to be modified taught by Scholander. One of ordinary skill in the art would be motivated to combine the specific depolymerized and supersulfated heparin disclosed by Naggi et al. with the surface modified to have improved antithrombogenic activity taught by Scholander because Naggi et al. recites "It is also generally recognized that at the same degree of polymerization, the biological activity of polysaccharides increases with their sulfation degree," (column 3, lines 42-44).

Response to Applicant's Remarks:

Applicant's Remarks, filed on 11 Aug 2008, have been fully considered and not found to be persuasive.

The response to Applicant's remarks regarding Naggi et al. is as detailed above.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623